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Cycloaddition

Ketenedithioacetals as Surrogates for the Formal Insertion of Ketenes into Donor–Acceptor Cyclopropanes

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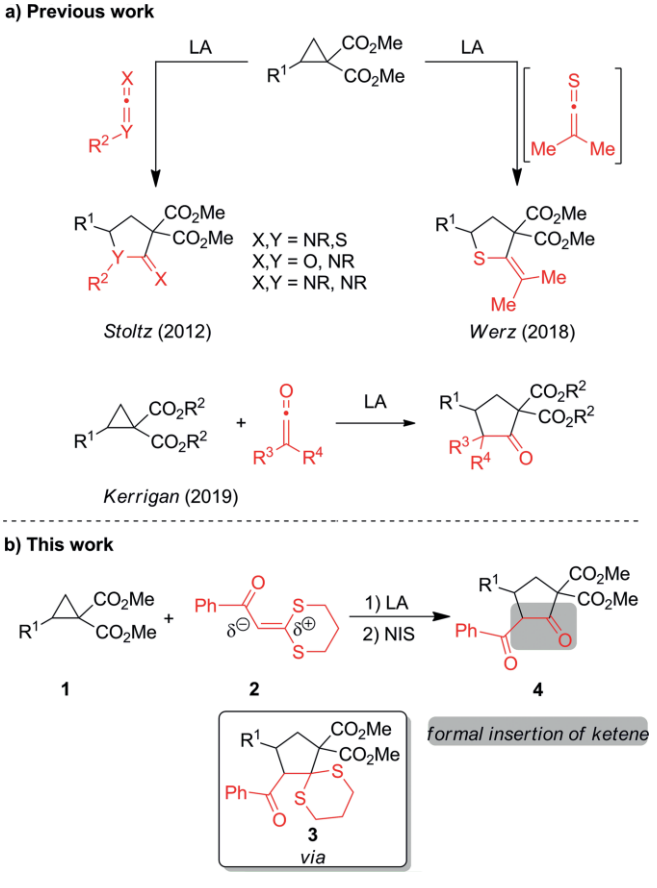
Abstract: The reactivity of donor–acceptor (D–A) cyclopropanes towards acceptor-substituted ketenedithioacetals was investigated. In a Lewis-acid-catalyzed (3+2)-cycloaddition, the corresponding dithiaspiro compounds were synthesized in good yields. The 1,3-dithiane unit, a masked keto functionality, was cleaved by *N*-iodosuccinimide. Thus, this two-step process represents a formal insertion of an acceptor-substituted ketene into a D–A cyclopropane.

During the last decade, donor–acceptor (D–A) cyclopropanes have become one of the most prominent buildings blocks for a three-carbon unit.[1] Pioneering work was performed by Wenkert and Reissig some 30–40 years ago,[2] since which numerous novel transformations have been developed to access complex carbo- and heterocyclic systems from these strained units. The strain energy of about 115 kJ/mol provides the thermodynamic driving force for all the ring-opening,[3] ring-enlargement[4] and cycloaddition[5] reactions of D–A cyclopropanes. However, the polarization of the bond to be cleaved, associated with the presence of electron-donating and electron-accepting residues, is of similar importance;[6] this polarization lowers the activation barrier for these processes and thus allows them to occur. The intrinsic push-pull effect can be further strengthened by complexation of the acceptor groups to Lewis acids, which remove even more electron density from the bond to be broken. Thus, numerous such transformations rely on Lewis acid catalysis.

Whereas π-systems such as olefins,[7] alkynes,[8] aldehydes,[9] imines,[10] nitroso compounds[11] and thiocarbonyls[12] have been easily inserted into D–A cyclopropanes to yield the respective five-membered ring systems, the insertion of cumulated systems has only rarely been explored. In 2012 the Stolz lab disclosed a Lewis acid-mediated (3+2)-cycloaddition of D–A cyclopropanes with isocyanates, isothiocyanates and carbodiimides (Scheme 1a).[13] Later, the Wang group employed allene moieties in an intramolecular manner to furnish bicyclooctane scaffolds.[14] Our group used four-membered thioketones as a surrogate for the formal thioketene insertion.[15] Mechanistic studies have shown that a spirocyclic system is an intermediate in this transformation and a Lewis-acid catalyzed (2+2)-cycloreversion is the crucial step to access the exocyclic thioenolether. In contrast to thioketenes, ketenes are stable entities; however, they are moisture-sensitive and have to be pre-



Scheme 1. a) (3+2)-Cycloaddition reactions of D–A cyclopropanes and heterocumulenes. b) Our approach of using a ketene surrogate. LA = Lewis acid.

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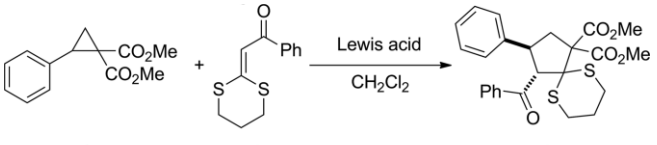
pared directly before use. Finally, Kerrigan realized the Lewis-acid-catalyzed insertion of disubstituted ketenes into D–A cyclopropanes in 2019.[16] This transformation led elegantly to the desired cyclopentanones in high yields (Figure 1a). Interestingly, different conditions afforded semicyclic enol ethers in which the carbonyl moiety was embedded into the ring system.[17]

Based on these previous findings, we were curious to find out whether it is possible to react D–A cyclopropanes **1** with the 1,3-dithiane-containing α,β-unsaturated ketone **2** in a (3+2)-cycloaddition.[18] It should be possible to convert the emerging dithiaspiro compounds **3** to the corresponding 1,3-diketones using NIS, ultimately leading to the formal insertion of a monosubstituted ketene into a D–A cyclopropane (Scheme 1b). Such a method would nicely complement the ketene insertion developed by Kerrigan and co-workers, which relies on disubstituted ketenes.

As a starting point for our investigations, we used D–A cyclopropane **1a** and two equivalents of the α,β-unsaturated ketone **2** in CH_2Cl_2 as model substrates for our envisioned transformation. Indeed, with $Sc(OTf)_3$ as Lewis acid the desired spiro compound **3a** was isolated in a good yield of 78 % after a reaction time of 3.5 h (Table 1, entry a). A change of the catalyst to $In(OTf)_3$ or $Sn(OTf)_2$ led to a significant decrease of the yield (50 % and 30 %, Table 1, entries b and c), whereas almost no conversion was observed when using $Yb(OTf)_3$, $Zn(OTf)_2$ and $Cu(OTf)_2$, even after extending the reaction time to 24 h (Table 1, entries d–f). When switching to metal halides as Lewis acid, only with $InBr_3$ was limited product formation detected (18 %, Table 1, entry g), while the use of $AlCl_3$ or TiF_4 yielded no product (Table 1, entries h and i). The best result was finally achieved by reducing the catalyst loading to 10 mol-% and slightly increasing the reaction time to 5 h. With these conditions the desired product was isolated in 90 % yield (Table 1, entry j). A reduction of the reaction temperature led to a lowering of the yield to 33 % (Table 1, entry k). If the concentration of the enone **2** was reduced to one equivalent, a slightly worse yield was observed (66 %, Table 1, entry l). The use of different Lewis acids had no significant influence to the diastereomeric ratio. Only a slight preference for the *trans*-isomer was observed.

Table 1. Optimization of the reaction conditions.[a]

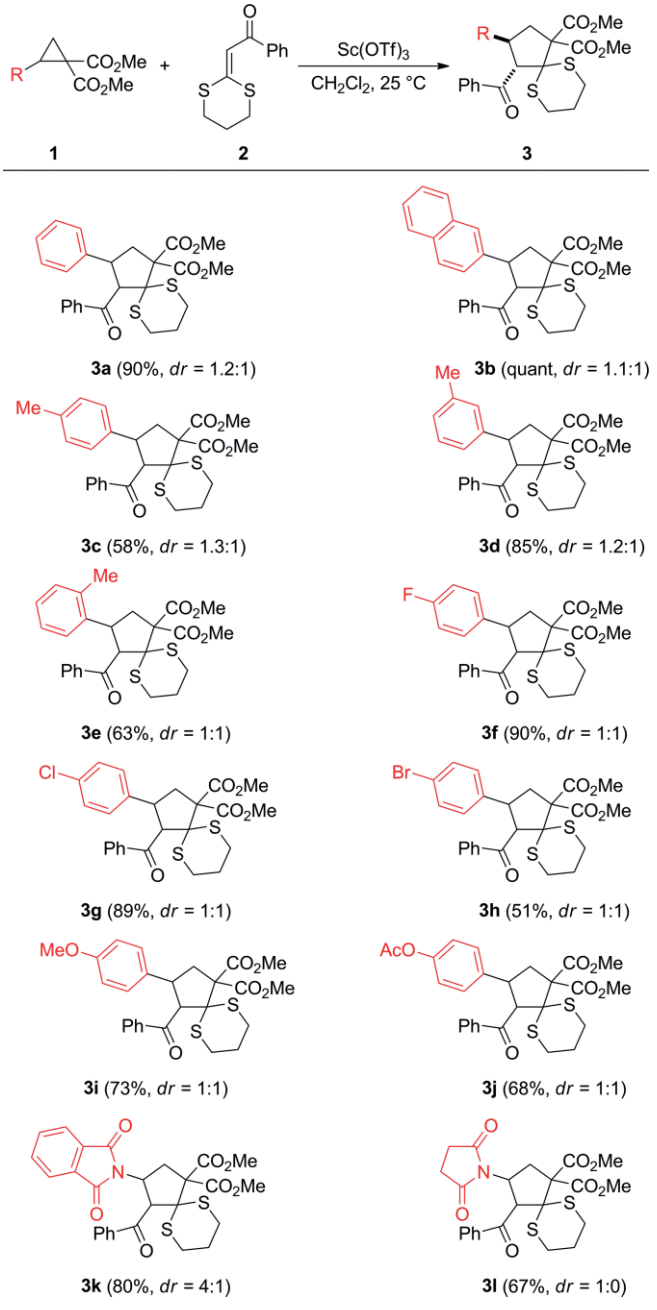


1a **2** **3a**

Entry	Lewis acid [mol-%]	*t* [h]	*T* [°C]	Yield **3a** (*dr*) [%]
a	$Sc(OTf)_3$ (20 mol-%)	3.5	25	78 (1.3:1)
b	$In(OTf)_3$ (20 mol-%)	3	25	50 (2.5:1)
c	$Sn(OTf)_2$ (20 mol-%)	4.5	25	30 (2.5:1)
d	$Yb(OTf)_3$ (20 mol-%)	4	25	–
e	$Zn(OTf)_2$ (20 mol-%)	24	25	–
f	$Cu(OTf)_2$ (20 mol-%)	24	25	traces
g	$InBr_3$ (20 mol-%)	5	25	18 % (1.0:1)
h	$AlCl_3$ (20 mol-%)	24	25	–
i	TiF_4 (20 mol-%)	24	25	traces
j	**$Sc(OTf)_3$ (10 mol-%)**	**5**	**25**	**90** (1.2:1)
k	$Sc(OTf)_3$ (10 mol-%)	6	0	33 (1.0:1)
l[b]	$Sc(OTf)_3$ (10 mol-%)	16	25	66 (1.5:1)

[a] Reaction conditions: **1a** (100 µmol), **2** (200 µmol), CH_2Cl_2 (1.0 mL), under Ar. Yields refer to the purified and isolated product. [b] **2** (100 µmol) was used.

With these reaction conditions in hand, we explored the scope of this formal (3+2)-cycloaddition with various D–A cyclopropanes **1**, leading to the spiro compounds **3** (Scheme 2). First, we increased the size of the π-system of the donor by using a naphthyl rather than a phenyl residue. This reaction worked



Scheme 2. (3+2)-Cycloaddition with various D–A cyclopropanes **1**. Reaction conditions: **1** (100 µmol), **2** (200 µmol), $Sc(OTf)_3$ (10 mol-%), CH_2Cl_2 (1.0 mL), r.t. Yields refer to the purified and isolated product. *dr* = *trans*-isomer:*cis*-isomer.

exceptionally well and delivered the desired product **3b** quantitatively. Next, we tested various substitution patterns of the phenyl residue. The transformations with a methyl substituent in *para*-, *meta*- and *ortho*-position gave the products in 58–85 % yield (**3c**–**3e**).

Furthermore, we tested halide substituents in *para*-position at the phenyl moiety. The reactions with fluoro, chloro and bromo substituents afforded the corresponding products in up to 90 % yield (**3f**–**3h**). Decoration of the system with an electron-donating *para*-methoxy group gave the product in a moderate yield of 58 % (**3i**). Attaching an electron-withdrawing group to the donor of the cyclopropane delivered the targeted product in a yield of 68 % (**3j**). Not only aryl moieties but also heteroatoms were suitable as donors in these reactions. The classical Waser cyclopropanes[19] with a phthalimide and succinimide as donor led to the corresponding spiro compounds with a yield of 67–80 %. Only with these special cyclopropanes was a noteworthy diastereomeric excess observed; the product **3l** was even isolated as a single diastereomer. In all other reactions the *dr* was not significant (approximately 1:1).

To unambiguously determine the relative stereochemistry of the synthesized products, we crystallized both stereoisomers of compound **3a**, and corresponding X-ray studies were carried out. The molecular structures of both stereoisomers are depicted in Figure 1.[20]

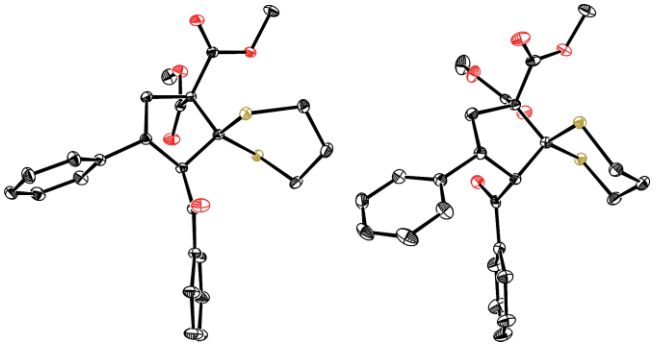
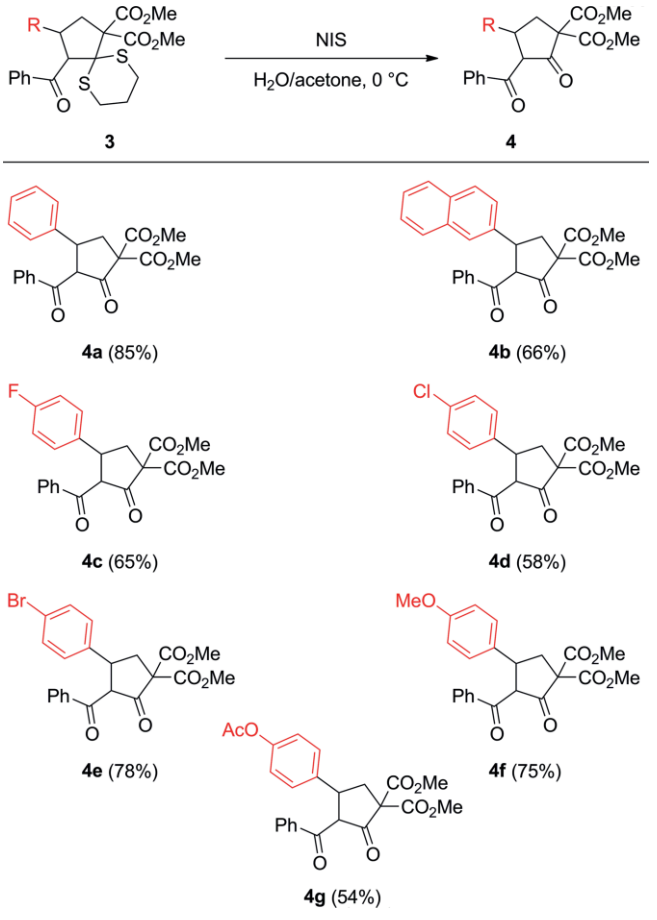


Figure 1. Molecular structures of *trans*-**3a** (left) and *cis*-**3a** (right) in the solid state.

Because it was our initial goal to develop a method for the formal insertion of ketenes using dithioketene acetals as appropriate surrogates, we wished to establish whether the 1,3-dithiane moiety can be converted into the corresponding carbonyl compounds. If this reaction was successful, the two transformations together would be the formal insertion of a ketene into a D–A cyclopropane. After trying several methods, it soon became apparent that only the use of a large excess of *N*-iodosuccinimide (NIS) in an H_2O/acetone mixture led to the desired conversion of the compounds **3** (Scheme 3).[21] The reaction ran smoothly with a phenyl group and delivered the diketone in a good yield of 85 % (**4a**) while compound **3b** was transformed in a moderate yield of 66 % to **4b**. The conversion of the halogen-substituted compounds **3c**–**3e** yielded the corresponding products (**4c**–**4e**) in 58–78 % yield. Additionally, the electron-rich derivative **3i** furnished diketone **4f** in 75 % yield, while product **4g** was isolated only in a moderate yield of 54 %. Interestingly, it transpired that this transformation could only be performed with the *trans*-isomer of **3**. If the *cis*-isomer was subjected to these reactions, no conversion was observed at all. The reason for such a striking discrepancy in the reactions of the two diastereomers remains obscure. It is noteworthy that all products **4** show a strong keto–enol tautomerism, as detected by NMR spectroscopy.



Scheme 3. Conversion of the dithiaspiro compounds **3** into the corresponding 1,3-diketones **4**. Reaction conditions: **3** (1.0 equiv.), NIS (8.0 equiv.), H_2O/acetone (0.1 M, 1:10), 0 °C.

In summary, we have successfully demonstrated the formal (3+2)-cycloaddition to D–A cyclopropanes of an acceptor-substituted ketene dithioacetal. The corresponding products were isolated in moderate to excellent yields. Both resulting diastereomers were structurally characterized by X-ray structure analysis. Furthermore, it was possible to convert the 1,3-dithiane moiety of the products into the corresponding ketones by using *N*-iodosuccinimide in an H_2O/acetone mixture. The resulting five-membered 1,3-diketones were isolated in good yields and showed a strong keto–enol tautomerism in their NMR spectra. This two-step process can be regarded as the formal insertion of an acceptor-substituted ketene into a D–A cyclopropane.

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Keywords: D-A cyclopropanes · Cycloaddition · Spiro compounds · Ketene insertion · Sulfur-containing compounds

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